Modeling neuro-immune interactions during Zika virus infection.

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Public Summary:
In 2015, a great increase in newborns with microcephaly among other birth defects were observed in Brazil, which was later linked to the Zika virus infections. Recent studies have shown that Zika virus causes the cell death of a specific cell type in the brain: neural progenitor cells (NPCs) by preferentially infecting them. The Zika virus is classically spread through a mosquito bite but it can also be vertically transmitted from the mother to the fetus. However it is unclear how this transmission occurs. Microglia are the macrophages of the central nervous system (CNS). Unlike other CNS cells, they are generated in the yolk sac during primitive hematopoiesis and they travel through the blood vessels to invade the CNS during embryogenesis. Considering the timing of their invasion, the authors hypothesized that microglia could also actively participate during the Zika infection, acting as a Trojan horse, by transporting the Zika virus during the CNS invasion. To test this hypothesis in a human context, they took advantage of the stem cell technology. They first generated the two relevant CNS cell types, NPCs and microglia, from human pluripotent stem cells and studied how they reacted when exposed to the Brazilian Zika virus. Then, they established a co-culture system where we could mimic the interactions of these two cell types in vitro. They found that microglia cells are able to engulf Zika-infected NPCs. In addition, the results show that when the Zika-infected microglia were put in contact with the NPCs, they were able to transmit the virus to the NPCs, suggesting that microglia might be indeed the culprit of transporting the virus to the CNS during neurodevelopment. Finally, using our co-culture system, they tested whether an FDA-approved drug, Sofosbuvir, was able to limit this virus infection of the NPCs in the presence of Zika-infected microglia. Importantly, Sofosbuvir significantly decreased the cell death of NPCs as well as the virus load in the NPCs. Altogether, the study suggests that microglial cells could be targeted to limit Zika virus spreading in the CNS. Thus, the co-culture system developed here is robust and useful to study neuro-immune interactions as well as to serve as a drug-screening platform to find new therapeutic compounds against Zika virus infections in a human context.

Scientific Abstract:
Although Zika virus (ZIKV) infection is often asymptomatic, in some cases it can lead to birth defects in newborns or serious neurologic complications in adults. However, little is known about the interplay between immune and neural cells that could contribute to the ZIKV pathology. To understand the mechanisms at play during infection and the antiviral immune response, we focused on neural precursor cells (NPC)-microglia interactions. Our data indicate that human microglia infected with the current circulating Brazilian ZIKV induces a similar pro-inflammatory response found in ZIKV-infected human tissues. Importantly, using our model, we show that microglia interact with ZIKV-infected NPCs and further spread the virus. Finally, we show that Sofosbuvir, an FDA-approved drug for Hepatitis C, blocked viral infection in NPCs and therefore the transmission of the virus from microglia to NPCs. Thus, our model provides a new tool for studying neuro-immune interactions and a platform to test new therapeutic drugs.